

Additive Manufacturing: The Next Generation of Scapholunate Ligament Reconstruction

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Abstract

Background Ligament reconstruction, as a surgical method used to stabilize joints, requires significant strength and tissue anchoring to restore function. Historically, reconstructive materials have been fraught with problems from an inability to withstand normal physiological loads to difficulties in fabricating the complex organization structure of native tissue at the ligament-to-bone interface. In combination, these factors have prevented the successful realization of nonautograft reconstruction.

Methods A review of recent improvements in additive manufacturing techniques and biomaterials highlight possible options for ligament replacement.

Description of Technique In combination, three dimensional-printing and electrospinning have begun to provide for nonautograft options that can meet the physiological load and architectures of native tissues; however, a combination of manufacturing methods is needed to allow for bone-ligament entheses. Hybrid biofabrication of bone-ligament tissue scaffolds, through the simultaneous deposition of disparate materials, offer significant advantages over fused manufacturing methods which lack efficient integration between bone and ligament materials.

Results In this review, we discuss the important chemical and biological properties of ligament entheses and describe recent advancements in additive manufacturing to meet mechanical and biological requirements for a successful bone–ligament–bone interface.

Conclusions With continued advancement of additive manufacturing technologies and improved biomaterial properties, tissue engineered bone-ligament scaffolds may soon enter the clinical realm.

Keywords

- bone–ligament
- interface
- regeneration
- tissue engineering
- additive manufacturing

Wrist injuries account for 3.6% of work-related accidents and approximately 20% of all emergency department visits, with an incidence rate of 3.8/10,000.^{1,2} Specifically, injury to the

scapholunate interosseous ligament (SLIL) can result in pain, instability, and eventual loss of mobility and arthritis. As one of the primary stabilizing structures in the wrist, the SLIL is

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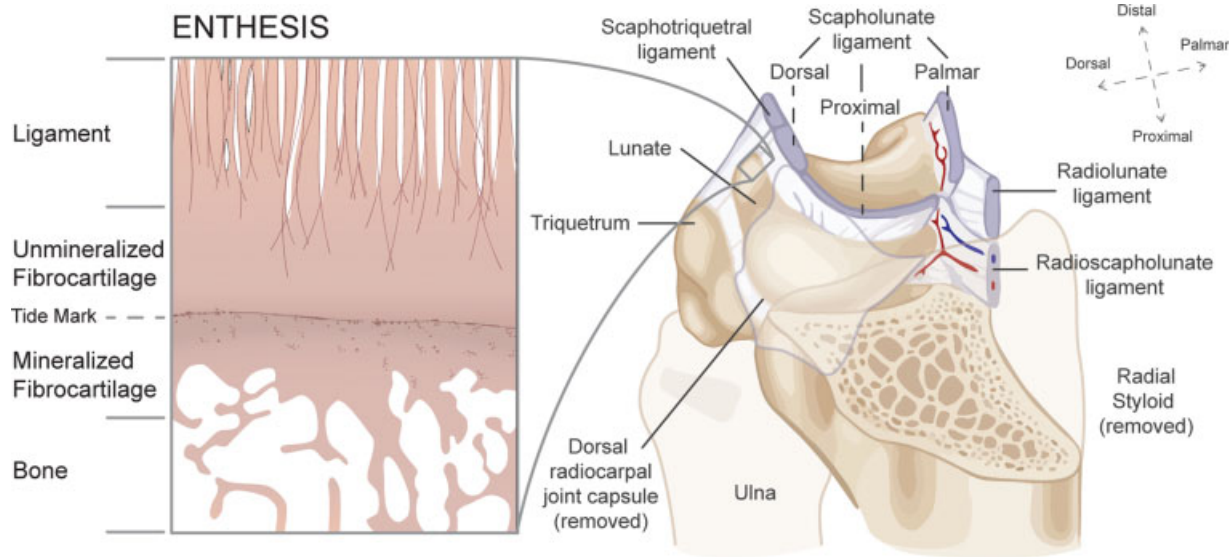


Fig. 1 Scapholunate interosseous ligament (SLIL) from radial perspective and bone ligament enthesis diagram. In this image the radial styloid region has been removed. The SLIL forms a C-shaped complex, which is open distally at the level of the midcarpal joint. The SLIL is composed of three segments: dorsal, proximal, and palmar. While heterogeneous in structure across each segment, bone-ligament enthesis is marked by four distinct regions (ligament, unmineralized fibrocartilage, mineralized fibrocartilage, and bone) which dynamically transfer forces across the joint.

often damaged as a result of a wrist hyperextension injury due to falls, sports, or other high energy trauma. Disruption to the SLIL with associated wrist instability leads to radiocarpal arthritis within 5 years of injury and eventual scapholunate advanced collapse.³

To restore joint function, ligament repairs can be accomplished utilizing a myriad of techniques from primary ligament repair and pinning, to dorsal capsulodesis, or reconstruction with screw fixation, tendon, or bone–ligament–bone (BLB) grafts.^{4–8} As a reconstructive material, autograft tissue has the advantage of matching physiological structure and mechanical strength at the risk of donor-site morbidity.⁹ However, high stress concentrations at the bone/tendon interface, and a lack of tissue integration between highly tensile ligament and highly compressive bone, can lead to failure and recurrent wrist instability after repair.^{10–20} Nonautograph options are available, but lack the ability to restore bone–ligament enthesis.

In an attempt to restore natural carpal kinematics, BLB constructs focus on restoring long-term joint structure and stability through whole ligament implantation.^{21–23} Specifically, BLB constructs maintain robust bone–ligament interfaces while simultaneously providing secure implantation through bone anchors. However, the limited supply of donor bone–ligament options and mixed clinical outcomes have led to an increased demand for tissue-engineered scaffold replacements.²¹ Recent advancements in tissue alternatives have focused on scaffold development with tailored mechanical and biochemical properties. Yet there still exists an unmet need for hybrid and multiphasic materials that combine spatial, mechanical, and biological activity. To achieve the hierarchical tissue gradients necessary for BLB reconstruction, different manufacturing modalities must be considered. Additive manufacturing (AM), through the layer-by-layer deposition of synthetic or natural materials,

promises to generate mechanically integrated composites which can be surgically implanted as whole or partial bone constructs while allowing for tissue regeneration and integration with the carpal bones. The SLIL represents an important engineering challenge, due to the complex anatomical structure and the difficulty in achieving long-term stability, which positions it as a strong target for AM. In this review, the AM technologies for bone, ligament, and cartilage regeneration are analyzed and discussed. Biocompatible materials are described and relevant techniques are highlighted with special emphasis on the design of hybrid scaffolds which mimic the BLB enthesis (→ Fig. 1).

Scapholunate Anatomy

The complexity of the SLIL anatomy is an ideal example in order to present the challenges faced in repair or reconstruction of ligaments. As the bridge between the two carpal rows, the SLIL is composed of a gradient of intermingled tissues which are heterogeneous in their distribution across the scapholunate interval (→ Fig. 1). The dorsal segment (~3-mm thick, 5-mm length) is trapezoidal in shape and composed of high tensile strength bundles of transversely oriented collagen fascicles (20–200 nm diameter) surrounded by loose connective tissues containing arterioles, venules, and peripheral nerve fibers.²⁴ Distally, the dorsal segment merges with the dorsal scaphotriquetral ligament, often appearing to be an integral part of the dorsal intercarpal ligament. The palmar segment is thinner (1 mm), composed of collagen fibers oriented slightly oblique from palmar-ulnar to dorsal-radial. Proximally, the palmar segment combines with the radioscapholunate ligament while distally it is covered by the radioscapholunate ligament synovial membrane. The proximal segment of the SLIL has a wedge-shaped cross-sectional geometry, varies in thickness, and is

Table 1 Common additive manufacturing materials used in tissue-engineered bone and ligament scaffolds

Material	Examples	Advantages	Disadvantages	Cell properties
Ceramics	Hydroxyapatite (HA) Calcium phosphate (CaP) Bioactive glass	<ul style="list-style-type: none">• Similar composition to bone• Strong integration with host tissue• Several delivered modalities	<ul style="list-style-type: none">• Brittle/low ductility• Extended degradation rate• Not compatible with cell encapsulation	Osteogenic
Synthetic polymers	Polycaprolactone (PCL) Poly (lactic-co-glycolic acid) (PLGA) Polymethyl-methacrylate (PMMA) Poly (propylene fumarate) (PPF)	<ul style="list-style-type: none">• Consistent product/properties• Modifiable material properties (physiochemical and mechanical)• Wide range of degradation	<ul style="list-style-type: none">• Often hydrophobic• May lack necessary mechanical properties• May contain cytotoxic agents	Fibrogenic Chondrogenic Osteogenic
Natural polymers	Collagen	<ul style="list-style-type: none">• Derived from extracellular matrix• Good biocompatibility• Good cell affinity• Biodegradable	<ul style="list-style-type: none">• Pathological impurities• Rapid degradation• Limited mechanical properties (without modification)	Fibrogenic Chondrogenic Osteogenic
Hydrogels	Glycosaminoglycans/hyaluronic acid (HLA) Polyethylene-glycol (PEG)	<ul style="list-style-type: none">• High water content• Modifiable mechanical properties• Controlled release• Easy 3DP patterning	<ul style="list-style-type: none">• Optimization of printing parameters• Limited mechanical properties• Uniform cell loading• Difficult physical manipulation	Chondrogenic

Abbreviation: 3DP, three-dimensional printed.

composed almost entirely of anisotropic fibrocartilage devoid of neurovascular bundles. It is difficult to distinguish between articular cartilage and the fibrocartilage of the proximal SLIL as they blend together at the articulating margins of the scaphoid and lunate.^{24–26} In its insertion into the scaphoid and lunate, the enthesis zones of the SLIL are composed of unmineralized and mineralized fibrocartilages which merge with cancellous bone. A composite tissue with highly rigid ceramic hydroxyapatite (HA) reinforced by a collagen network enables a mechanically graded transition from ligament to bone tissue while also balancing the various forces that may be applied to the joint.^{27,28} As the primary target for BLB scaffolds in the wrist, the SLIL is referenced for its anatomical and mechanical behavior; however, clinical outcomes are relevant to BLB interfaces throughout the body.

Development of Biocompatible Materials

To match the mechanical, biological, and organizational properties for ligament and bone scaffolds, commonly used materials such as ceramics, polymers, and biological molecules have been proposed. Of primary interests are materials designed specifically for bone, ligament, and cartilage tissues (►Table 1), which range from rigid mineral matrices to soft hydrogels to recapitulate the transition of tissue across the joint. For bone regeneration, ceramic biomaterials such as HA/calcium phosphate (CaP) and bioactive glass are ideal candidates.^{29–31} These materials aid in restoring the lost biological function over polymers alone due to their similar composition to bone mineral while also stimulating cell proliferation and differentiation.^{29,30} HA, in particular, has shown significant bioactivity among osteoblastic cell lines resulting in effective adhesion, proliferation, and tissue production.³¹ The relatively low degradation rate of HA facilitates extensive tissue remodeling and mechanical support; however, brittleness and low ductility limit sole use as a bone replacement. Synthetic polymers such as polycaprolactone (PCL), the copolymer poly(lactic-co-glycolic acid) (PLGA), polymethyl-methacrylate (PMMA), and poly(propylene fumarate) (PPF) have been used in conjunction with ceramics or as replacement bone scaffolds. Their highly modifiable mechanical and manufacturing properties allow for controlled production of scaffolds, but the reduced mechanical strength is often unsuitable for sole use as cancellous bone (40–150 MPa).^{32,33} As a processed material, cellular growth on HA incorporated into both PCL and collagen scaffolds has shown the ability to promote proliferation of human mesenchymal stem cells (MSCs) and induced their osteogenic differentiation.^{34,35} Overall, it is the complement of ceramic and polymeric materials which offers the greatest promise for bioactive bone scaffolds. In combination, polymeric and ceramic scaffolds increase the ease of fabrication, provide faster degradation and remodeling, and tunable tensile properties while preserving the mineral rigidity of natural bone.³⁰

In comparison to highly compressive bone, the predominant characteristic of ligament is its ability to withstand significant tensile loads (10–17 MPa).^{36,37} To accommodate

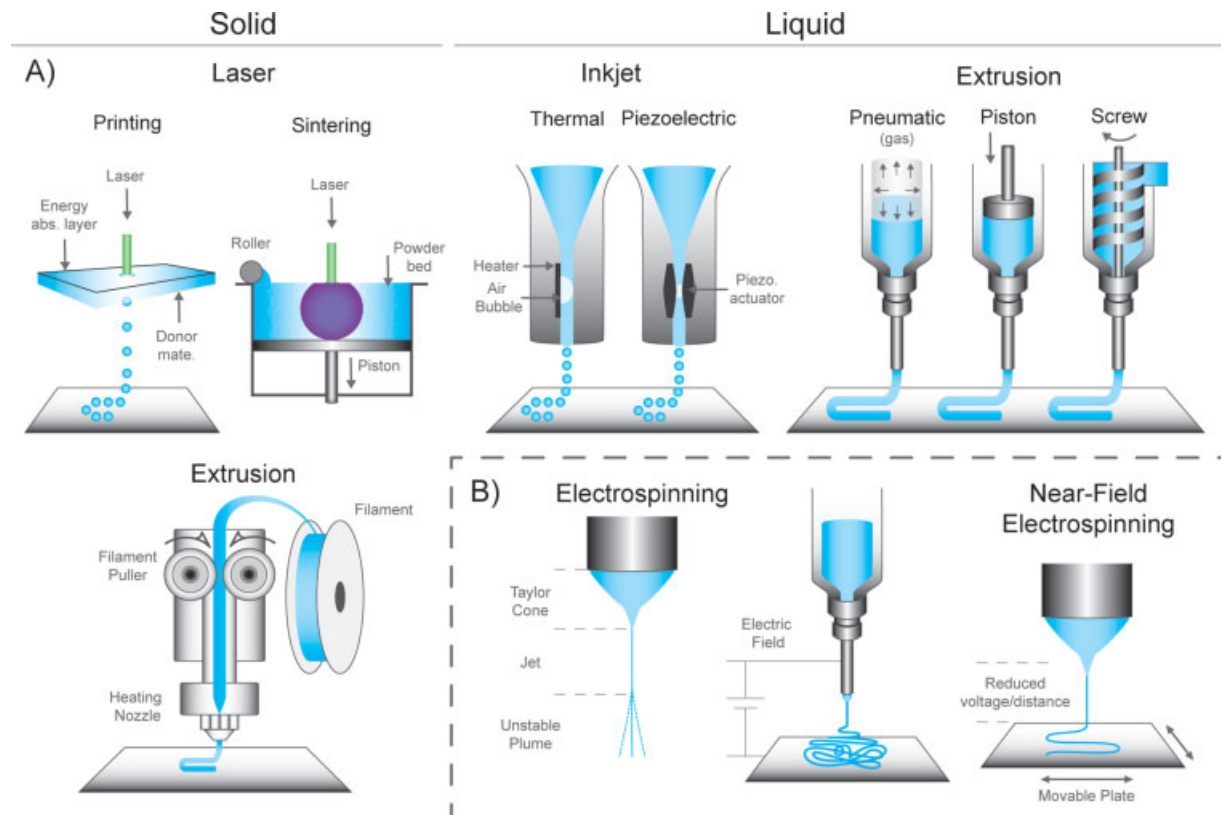


Fig. 2 Diagram of additive manufacturing modalities. (A) 3D printing technologies: laser-assisted printing, inkjet printing, and extrusion-based (solid and liquid) printing. (B) Standard electrospinning and near-field electrospinning modes.

such forces, polymer materials PLGA and PCL are often used alone or in combination with decellularized proteins such as collagen I to provide ductile tensile support while also guiding the elongation and bundling of fibers for ligament regeneration.^{38,39} In comparison to PLGA, PCL is relatively more hydrophobic and tends to offer greater mechanical properties (10–60 MPa)⁴⁰ while allowing for cellular compatibility with surface modification.^{38,39}

Often overlooked, an interfacial fibrocartilage region exists between the disparate bone and ligament zones, and serves to transmit forces across the joint.⁴¹ This region has been implicated in joint nonunion and collapse.⁴² Primarily composed of collagen and glycosaminoglycans such as hyaluronic acid (HLA), this region helps to anchor the ligamentous fibers within the rigid bone network.⁴³ With large quantities of hydrophilic gel matrix, this region is largely avascular but provides a critical role in tissue damage and remodeling.⁴¹ Commonly used materials for regenerating cartilage include synthetic polyethylene glycol (PEG)/PEG acrylates and natural materials including gelatin/gelatin methacryloyl and HLA.^{33,44,45} Used by themselves or in combination, hydrogel materials offer high water content and diffusion characteristics for biological molecules and cell migration.⁴⁵

Cell Sheet Formation

Early efforts to address the gradient BLB interface focused primarily on co-culturing of cell sheets to simultaneously

produce disparate tissues in an integrated fashion. Co-culturing includes mixing a monolayer of cell types that exist at the interface—typically osteoblasts and fibroblasts. This method has shown some success in allowing for cell migration and proliferation, spatially distinct matrices, and expression of protein biomarkers specific for each tissue type.^{46–50} A recent study discovered scaffolds seeded with co-cultured osteogenic and endothelial-differentiated MSCs enhanced osteogenic and angiogenic factor expression and biomineralization both in vitro and in vivo.⁵¹ Alternatively, Carvalho and colleagues fabricated PCL fiber mats for the co-culture of MSCs and human umbilical vein endothelial cells that significantly promoted proliferation of seeded MSCs and their osteogenic differentiation in vitro.⁵² Unfortunately co-culturing by itself often results in mechanically inferior tissues without significant mechanical conditioning to increase the deposition of load-bearing materials.

Additive Manufacturing

AM is a collective of computer-aided design techniques to fabricate layer-by-layer constructs. Through use of computed tomography (CT), AM can create patient-specific solid models of bone and soft tissue using materials tuned to the mechanical and chemical characteristics of each tissue. To form and shape biomaterials into reliable scaffolds with the appropriate mechanical and architectural features for the replacement of bone, ligament, and cartilage, AM utilizes several different modalities. Extrusion-based three-

dimensional (3D) printing (3DP) and electrospinning (ESP) are the most common AM methods for tissue engineering and have proven the most effective when developing composite scaffolds of bone, ligament, and the complex BLB tissue interface; however, several other methods have been employed (►Fig. 2).

3D Printing

3D printing (3DP) technologies can be categorized into liquid or solid material categories with laser-assisted/sintering, inkjet printing, or extrusion-based modalities (►Fig. 2). Common to all these technologies is the use of CAD software or digital images, which provide the model for building a replacement scaffold. Because of the diversity of materials, economy, and its capacity to print porous structures,⁵³ extrusion-based printing is the most widely applied technique for potential BLB regeneration. As the name indicates, extrusion printing involves the controlled extrusion of a material through a printer head onto a build plate. In most systems, mechanical movement or a pneumatic pressure enables the extrusion of a polymer leading to the deposition of a filament, the dimensions of which can be adjusted by altering the printing parameters (e.g., viscosity, temperature, extrusion rate, velocity, etc.).

Electrospinning

ESP is an AM technique that uses electrical charge to modify fiber diameter, order, and length. In ESP, a polymer solution

is placed in a syringe with a metallic needle that is held some distance (5–25 cm) from the surface of a conductive, flat collector plate (unaligned fibers) or rotating mandrel (aligned fibers). A high voltage (20–35 kV) is applied across the needle and collector, which draws the polymer from the syringe producing long-strand nanofibers to collect on the surface. Due to its ability to produce long continuous fiber strands, ESP is the preferred AM modality to fabricate tendon/ligament constructs for effective tensile loading.^{54–56} However, while ESP can create small-diameter fibers, this method of fabrication has difficulty in creating controlled architectures of a variety of shapes and thicknesses. In comparison, near-field ESP (NFE), a variation of standard ESP, uses a reduced needle to collector distance (<3 mm), reduced voltage (<3 kV), and movable build plate to control fiber deposition. Given the close distance, NFE fibers are typically of larger diameter compared to standard ESP techniques but can be highly aligned for controlled scaffold characteristics (►Fig. 2).^{57–64}

Tissue Scaffolds for Bone and Ligament

To achieve the high mechanical loading behavior of bone, sintering techniques are often used to fabricate ceramic scaffolds with a primary emphasis on bone biomechanics.^{31,47,65} As an example of bone sintering, Zeng et al³¹ used a proprietary polymer in combination with HA in a two-step sintering process to create a prosthetic for bone

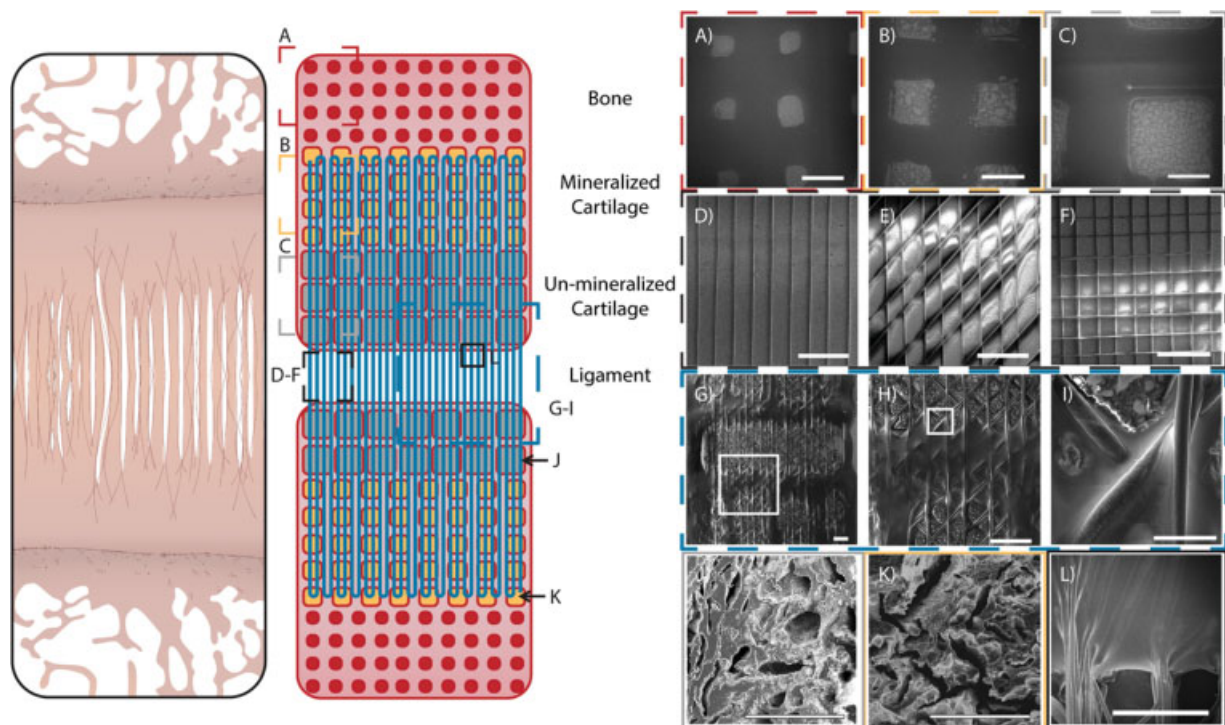


Fig. 3 Diagram of bone–ligament–bone tissue interface gradient with representative SEM images of corresponding fabrication materials. Scanning electron micrographs of (A–C) single-layer composite PPF scaffolds with increasing pore size, scale: 500 μ m. (D–F) Single-layer PCL (D: 0°, E: 0–45°, F: 0–90° biaxial) NFE scaffolds, scale: 500 μ m. (G, H) Single-layer 3D-printed PPF and NFE PCL ligament enthesis scaffolds, white box indicates zoomed-in image from previous image, scale: 500 μ m. (I) Scale: 100 μ m. (J) PEGDA cartilage scaffold, with (K) 10% hydroxyapatite inclusion, scale: 250 μ m. (L) Integration of PCL ligament scaffold interface with bone-PPF, scale: 500 μ m. 3D, three-dimensional; NFE, near-field electrospinning; PCL, polycaprolactone; PPF, poly(propylene fumarate).

tissue defects. First, the material was 3D printed into a grid shape then the materials were sintered, resulting in high cell viability and good 2-day cell proliferation when seeded onto scaffolds. While this technique has proven to allow for high compressive strength bone scaffolds, its manufacturing methods limit architectural control, do not allow for cell seeding during fabrication, and do not provide a gradual transition from bone and mineralized fibrocartilage phases into the ligament phase. To achieve more homogenous scaffolds, extrusion-based methods have been used to combine polymer and mineral components for higher resolution porous architectures, similar to cancellous bone.⁶⁶

In the early 2010s, researchers began fabricating more structurally complex gradient scaffolds using 3DP and other ESP-based AM platforms.^{54,56–59,61–72} Each manufacturing platform has deposition characteristics appropriate for targeting different phases of the bone–ligament interface. Diaz-Gomez et al⁶⁸ printed gradient scaffolds using PCL, tricalcium phosphate (TCP), and HA. They showed that composites of PCL with HA and TCP and gradient structures resulted in higher tensile moduli than PCL alone. Sprio et al⁵⁶ created graded scaffolds of the bone–cementum–periodontal ligament interface by ESP of an iron-doped HA and cellulose acetate composite material simulating the structure of the cementum. The composite maintained cell viability and produced similar pore sizes to native bone, but resulted in a discontinuous, disordered product due to the uncontrolled fiber depositions of standard ESP techniques. Gwiazda et al⁷³ also used ESP to create a PCL BLB scaffold. They were able to control pore size, had cell alignment along the ligament fibers, and replicated some of the mechanical properties of ligament. However, their scaffold showed a lack of architectural control with low tensile strength. Furthermore, this method did not allow for creation of large dense boney materials. To create organized, ordered fibers with controllable structure, recent NFE techniques are becoming increasingly more common. For example, He et al⁵⁸ combined HA and PCL to fabricate mats with controllable structure and distinct fibers with consistent diameter. Given the ability to control scaffold architecture, NFE techniques provide an intermediate to fiber printing while utilizing controlled fabrication constraints, similar to 3DP.

Hybrid Biofabrication for Bone–Ligament Tissue Scaffolds

For predictable BLB regeneration to occur, hierarchical tissue formation with appropriate interfacial connection is required. Equally important is establishing sufficient strength and mechanical integrity for ligament stability, which is determined by fiber orientation and incorporation into bone and cartilage phases. As knowledge of the cellular, mechanical, and chemical needs of the native tissue interface improves, researchers have begun combining techniques to produce multiphasic material scaffolds.^{72,74–78} Combining manufacturing platforms enables multiscale, multimaterial deposition to obtain complex biomechanical and biochemical responses for multiple interfacial tissue types. Xu et al⁷⁷

targeted cartilage tissue interfaces by ESP of PCL followed by 3DP a cell-based solution of chondrocytes, fibrinogen, and collagen with gelation by printing of thrombin. The authors found that this composite resulted in high cell viability and tissue production with greater tensile strength than alginate, collagen/fibrin, or ESP of PCL alone; however, composite structures lacked a well-defined-oriented fiber structure. Similarly, Costa et al⁷² developed a complex scaffold for periodontal ligament regeneration by 3DP of PCL containing TCP coated with CaP. They found that MSCs had high cell viability and high cell mobility within the scaffold. The CaP coating encouraged mineralization, and after implantation for 8 weeks, found no immune response and good tissue integration. However, they found no differentiation between the ligament and bony cells after 2 weeks and did not examine the space between the bone and ligament. More recently, Criscenti et al⁷⁶ targeted triphasic scaffold development for regenerating the bone–ligament interface by 3DP of PCL then melt-ESP PLGA onto an exposed portion of the 3DP bone section. They found that their scaffolds had three distinct sections: bone, mixed, and ligament, with mechanical behavior similar to native tissue. The mixed region had the highest resistance to tensile loads and resulted in the best proliferation of human MSCs. He et al⁵⁸ also created a hybrid scaffold that encapsulates all four sections of the bone–ligament interface without using AM. They created an entheses mold with TCP–PCL bone anchors intermixed with parallel polylactic acid (PLA) ligament fibers. By sintering TCP, then bonding the PLA fibers by and casting PCL into the remaining zones, they found that there was no clear material interface between the scaffold regions. However, their mechanical properties did not recapitulate the required loading for ligament replacement. Overall, the discrete fabrication of each material phase using 3DP/ESP-based platforms and assembly of those phases into composite structures yielded promising interfacial scaffold options. However, a system that enables continuous fabrication of a composite scaffold using a combination of these platforms may permit the best solution for optimal functional gradients.⁷⁸

To provide for more controlled interface production, our group (led by co-author C.S.) has recently begun 3DP and NFE hybrid scaffolds, using a single-device multihead printing system that more closely mimics the ligament entheses zone (–Fig. 3).⁶⁷ With 3DP PPF as a bone phase, 3DP poly(ethylene glycol) diacrylate (PEGDA) as a cartilage phase, and NFE PCL as a ligament phase, we have shown sufficient mechanical stability of the bone and ligament phases while allowing for integration between adjacent phases. Additionally, all materials maintained high cell viability and ligament fiber alignment affected cellular attachment and migration. However, continued work focusing on cellular differentiation and controlled tissue production will determine the overall effectiveness in the ability of such hybrid scaffolds to produce long-term BLB scaffolds for ligament reconstruction.

Overall, the combination of multiphasic scaffolds is required for effective fabrication of bone–ligament entheses, as well as the creation of relevant mechanically rigid replacements that preserve the bioactive and remodeling behavior

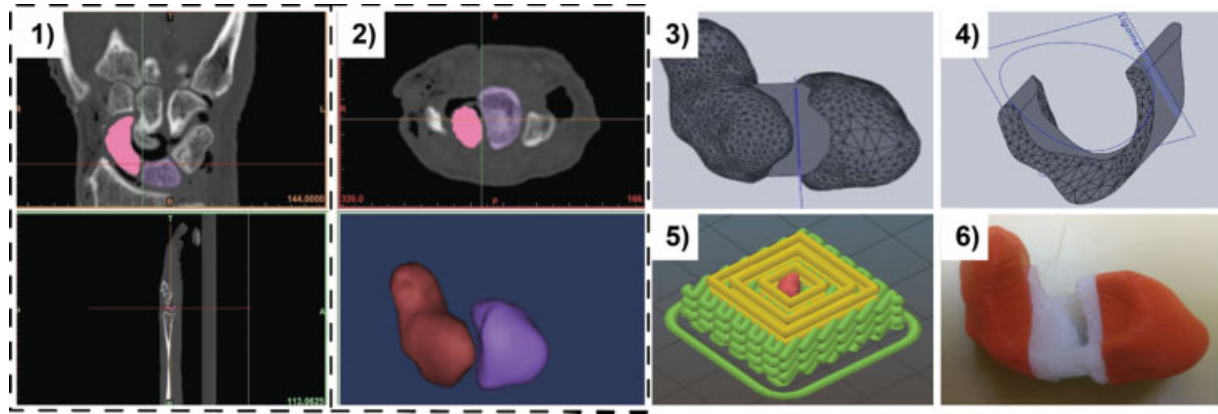


Fig. 4 Representation of the scan-to-print process for an additively manufactured (AM) scapholunate graft with (1 and 2) CT scan data converted to a 3D model. The modeling software is used to reproduce the U-shaped scapholunate ligament bridging the scaphoid and lunate bones (3). A virtual cut encompassing the ligament and ~10 mm of the scaphoid and lunate entheses (4) is then isolated from the model. A slicing software is used to identify the material phases and generate the g-code needed for AM (5). The scaphoid and lunate bones plus bone–ligament–bone (BLB) graft is represented in (6) with a 3D printed scaphoid and lunate model (red) and composite BLB graft (white) representing how the graft may be surgically implanted. 3D, three-dimensional; CT, computed tomography.

of native tissues. By combining relevant 3DP methods with bioactive ceramics, bone phase materials with optimal compressive strength and remodeling abilities can be fabricated. Through use of ESP techniques, fabrication of ordered high tensile strength ligament materials with cellular attachment and elongation similar to native ligament are being developed. Finally, in combination with collagen matrices, either natural or synthetic, realistic cartilage interfaces with good tissue remodeling are beginning to be realized.⁷⁶ At this point, the true challenge lies in development and optimization of integrated AM systems for fabrication of complete gradient scaffolds while preserving appropriate resolution for tissue architectures and mechanical strength within each phase.

Scan-to-Print Manufacturing

Along with the development of more advanced AM technologies, musculoskeletal imaging and characterization techniques have also advanced considerably allowing for realization of customized, patient-specific implantable scaffolds to be developed. The methodology described in ►Fig. 4 is used by the C.S. group to fabricate BLB scapholunate scaffolds for evaluation as an implantable graft. In overview, the premise of a scan-to-print pipeline begins with CT and/or magnetic resonance scanning of the damaged tissue along with computation of the native tissue density and organization.^{79,80} From this assessment a 3D model can be developed, and the soft tissue attachments reconstructed. To aid surgical reconstruction, the graft implant can be isolated and processed for printing. Overall, the combination of AM techniques with patient-specific graft development may offer greater flexibility for surgical reconstruction through individualized anatomical reconstruction and greater integration of implanted materials.⁸⁰

Conclusion

The main challenge in ligament reconstruction is the unpredictable degree of tissue healing after repair or reconstruction. By combining cells and bioactive factors with implantable materials in an organized and integrated fashion, a more controlled repair and regeneration of tissues may be achieved. The increasing knowledge of the biological principles underlying bone, ligament, and interfacial tissues and the development of novel regenerative approaches calls for different manufacturing methods. The ability to create constructs with precisely defined biological and biomechanical properties and patient-specific architectures in an automated and reproducible manner makes AM a desirable option for production of engineered implantable tissue replacement alternatives.

With the complex recapitulation of wrist anatomy and a true clinical need for a better scapholunate bone–ligament replacement, researchers have been creative in addressing the challenges to manufacture implantable BLB scaffolds. Biosafe materials must be developed to match the mechanical and chemical properties while also allowing biological proliferation, migration, and sterilization for implantation. Scaffolds need to be fabricated in an easily accessible, easily customizable way, while mitigating manufacturing error and tissue inconsistencies. The scaffolds must interface with the human body, regenerate the bone–ligament entheses, and achieve the desired surgical outcomes. While the field of interfacial gradient engineering is still in its infancy, much preliminary work has been done to prove the efficacy of fabricating multimodal gradient scaffolds using biocompatible materials, which can guide cellular differentiation and tissue production. Future work will depend on optimizing and controlling cellular organization and sufficient tissue integration to regenerate the BLB entheses. As a result, research endeavors are likely to focus on material

modification and incorporation of bioactive molecules, resulting in rapid cellular differentiation and tissue reorganization. In conjunction with recent advancement in AM, biological activation will help to speed the process of scaffold incorporation within the reconstructed joint and result in better patient functional outcomes.

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Conflict of Interest

None declared.

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